Case Discussion in Blood Glucose Variability

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ABSTRACT

Stress-induced hyperglycemia has been associated with poor outcomes and death in critically ill patients. Blood glucose (BG) variability, a component of stress-related hyperglycemia has recently been reported as a significant independent predictor of intensive care unit and hospital mortality. We sought to evaluate three cases in which intensive insulin therapy was administered using a standardized insulin dosing protocol to normalize the BG and reduce glycemic variability. Point-of-care BG values and other clinical measures were obtained from the medical record of three patients who received intensive insulin therapy. This was a convenience sample of three patients where the BG level had stabilized on a consistent intravenous insulin dose rate for up to 20 hours in a surgical trauma intensive care unit. Data were collected manually and electronically using the Remote Automated Laboratory System-Tight Glycemic Control Module (RALS-TGCM®) BG management and monitoring system. Each case presentation describes a critically ill, nondiabetic patient, requiring continuous intravenous insulin therapy for hyperglycemia. In each instance, BG variability was present in a worsening patient condition after a period of normalization of hyperglycemia with intensive insulin therapy. Although decreasing BG variability is an important aspect of hyperglycemia management, new onset events of variability may be a sentinel warning or occur as a physiologic response to a worsening patient condition. If so, these events warrant rapid investigation and treatment of the underlying problem.

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Although the causes remain unclear, hyperglycemia is an important, pathophysiological marker in both diabetic and nondiabetic patients requiring intensive care (Falciglia, 2007; Umpierrez, 2007). Intensive insulin therapy as an acute care intervention to normalize blood glucose (BG) is an effective means to reduce hyperglycemia-related morbidity and mortality (Furnary & Wu, 2006; Krinsley, 2004; Reed et al., 2007; Van den Berghe et al., 2006). The benefits of intensive insulin therapy are felt to be related to the reduction and maintenance of the BG level within a range of 80–110 mg/dl (4.4–6.1 mmol/L) (4–6). However, recent evidence suggests that wide BG excursions, either high or low or within or outside of the target range might be an equally important parameter to monitor. These BG excursions or glucose variability (defined as coefficient of variance or standard deviation [*SD*] from the mean BG) have been found to be an independent predictor of intensive care and hospital mortality even in patients with normalized mean BGs (Egi, Bellomo, Stachowski, French, & Hart, 2006; Krinsley, 2007; Van den Berghe et al., 2006).

In this article, we discuss three patients to whom intensive insulin therapy was administered using a standardized insulin dosing protocol to normalize the BG. In these cases, the BG level had stabilized within the target BG range by administering a consistent intravenous insulin dose rate for up to 20 hours. The BG of each patient then began to rise, despite upward adjustment of the insulin dose as an attempt to treat the hyperglycemia. In each case, the rise in BG preceded the signs and symptoms of a new onset serious, life-threatening complication.

These patients were treated in the surgical trauma intensive care unit (ICU) at the University Hospital in San Antonio, Texas. University Hospital serves as the lead, level I, trauma center for 22 South Texas counties. The surgical trauma ICU is a 25-bed "open" unit with continuous faculty intensivist and resident coverage from The University of Texas Health Science Center at San Antonio. Intravenous insulin glycemic control protocols have been in place since 2004, with a target BG range of 80–110 mg/dl. Finger-stick BG

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tests are performed hourly, and patients are started on continuous intravenous insulin infusion when their BG exceeds 120 mg/dl on two occasions or 150 mg/dl on one occasion.

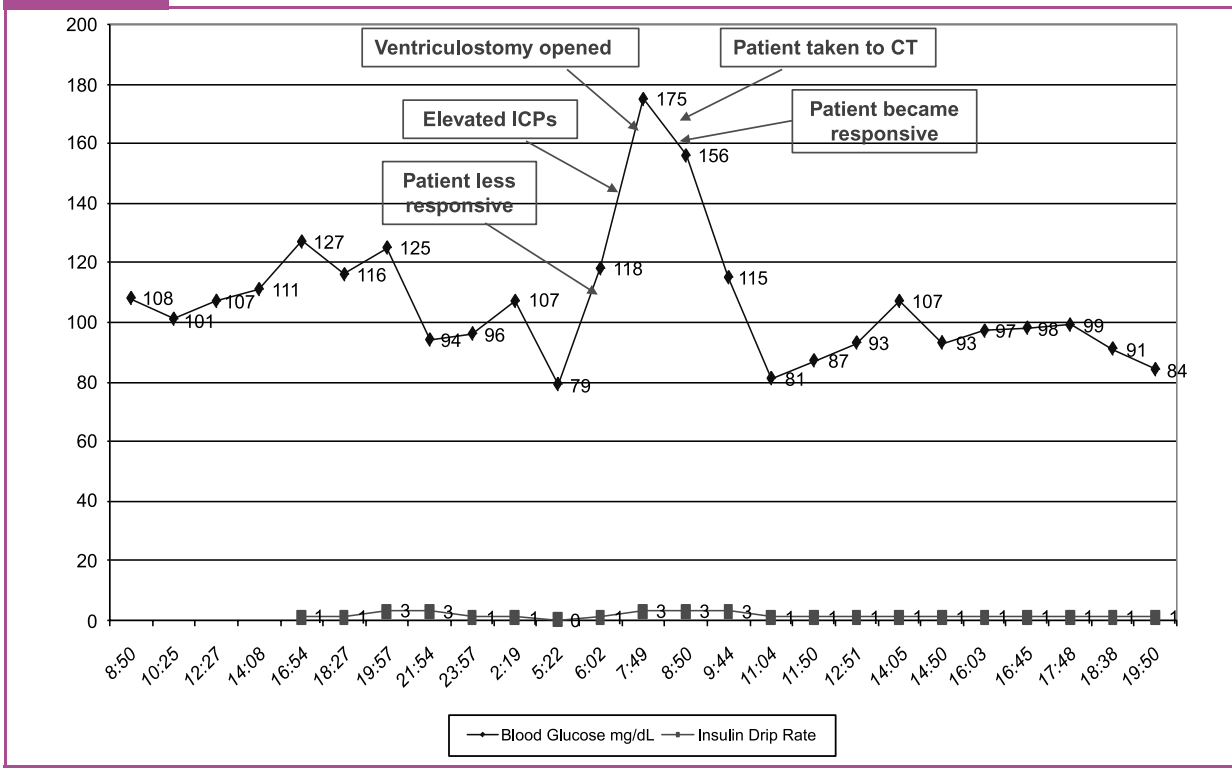
Case 1

This patient was an 18-year-old man involved in a motor vehicle collision. He sustained multiple injuries including pulmonary contusions, long bone fractures, and severe traumatic brain injury. His APACHE II score was 25 with a Glasgow Coma Scale (GCS) of 8. While undergoing an emergent exploratory laparotomy, a ventriculostomy was placed to monitor intracranial pressure (ICP); opening pressure was 10 cm H_2O. On admission to the ICU, the patient was mechanically ventilated and sedated with fentanyl and midazolam drips, and following commands with noxious stimulation, GCS of 8T. Admission finger stick BG was 108 mg/dl. Nursing staff monitored the patient's BG results every 1–2 hours (mean BG = 106 mg/dl, range 79–127 = mg/dl), initiating an intravenous insulin drip when BG became >120 mg/dl. At 6:00 a.m. on the second day, the patient was noted as being less responsive with a GCS of 2T, and at 6:45 a.m. the patient had a sudden spike in ICP. At 7:30 a.m., the ventriculostomy was opened to drain. The patient was taken to CT scan at 8:00 a.m.

In each of the 3 cases discussed, the rise in blood glucose preceded the overt appearance of signs and symptoms of new and potentially life-threatening complications.

The ventriculostomy was left open and drained a total of 20 ml of cerebral spinal fluid. At 8:20 a.m., the patient became responsive again and was able to follow commands with a GCS of 8T. Results from the CT revealed mild brain swelling. During the elevated ICP episode, the patient's BG level spiked to 175 mg/dl despite being stable within a normal glycemic range on minimal intravenous insulin dosing for nearly 24 hours from admission. Although the mean BG for this patient was 107 mg/dl, glycemic variation was 60 mg/dl (a factor of 2 *SD* from the mean, $P < .001$), which is clinically and statistically significantly different from the target (Figure 1).

FIGURE 1 **Blood Glucose (BG; mg/dl) and Intravenous Insulin Infusion Rate Time Series (Units/Hour) for Case Study 1**



Note. BG that had been stable in target trended upward and spiked when the patient experienced increased intracranial pressure (ICP). Once the ICP was relieved, the BG levels returned to baseline.

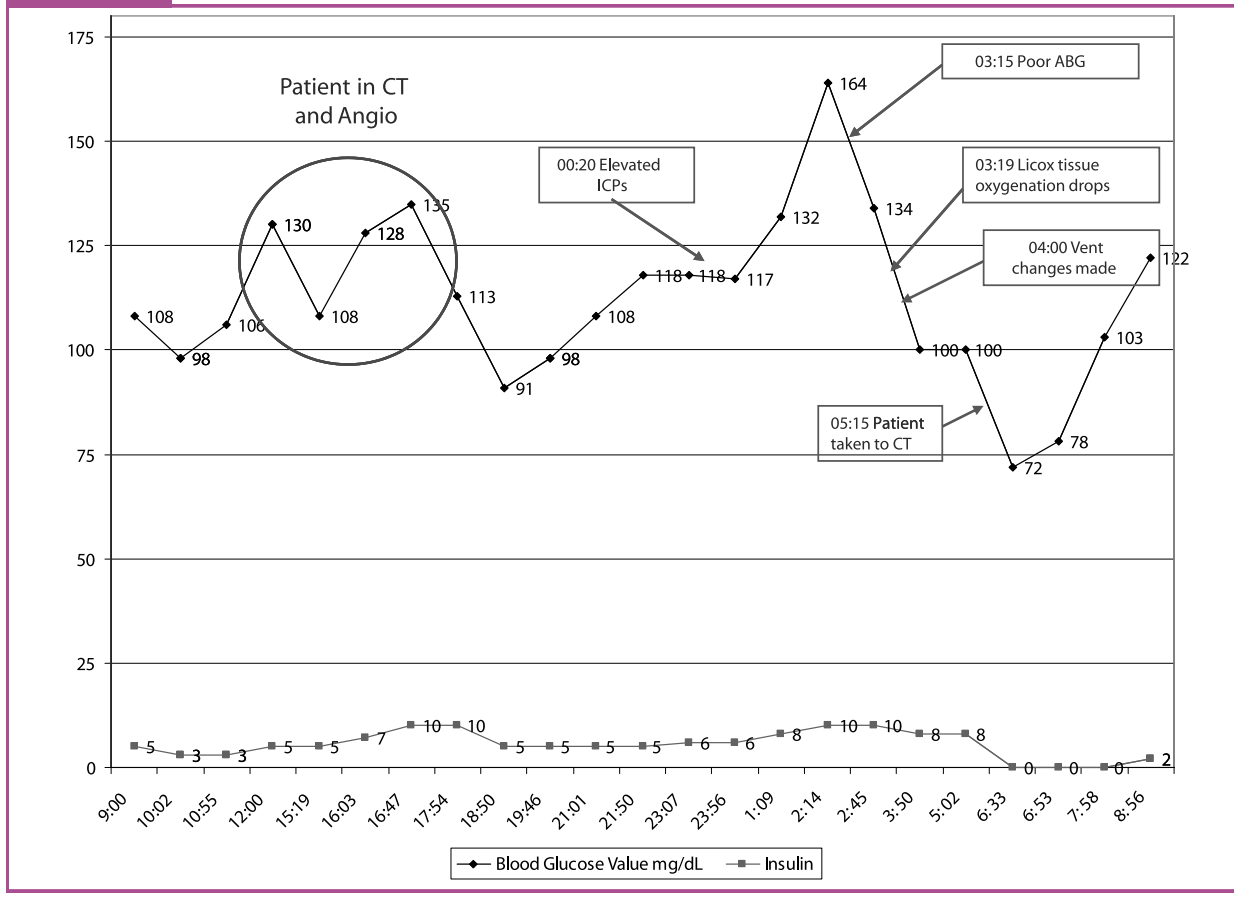
Case 2

A 25-year-old man was involved in a motorcycle collision and suffered an open skull fracture, diffuse subarachnoid hemorrhage, multiple rib fractures, and pulmonary contusions with a GCS of 2T. The patient was taken to the operating room for a craniotomy and irrigation to remove the hemorrhage. He was admitted to the ICU postoperatively with an APACHE score of 23 and a GCS 2T. At 12:20 a.m. on hospital day 6, the patient developed an elevated ICP, and at 12:45 a.m., a pentobarbital bolus was given and the pentobarbital drip rate was increased to lower brain metabolic needs. The patient's ICP continued to increase. In addition, the patient began to develop mild–moderate problems, with gas exchange characterized by mild hypoxemia and moderate hypercarbia. At 3:19 a.m., Licox tissue oxygenation was 23, and an additional bolus of pentobarbital was given. At 5:15 a.m., the patient was taken for a pulmonary CT scan, which revealed a pulmonary embolism had occurred. The mean BG for this patient was 112 mg/dl, with excursions of 20–50 mg/dl of hyperglycemia (1.5 *SD* from the mean, $P < .05$) on two occasions (Figure 2).

Case 3

This patient was a 67-year-old woman on warfarin who experienced a closed head injury from a fall with a GCS of 12. Upon admission to the hospital, the patient had a declining neurological status, which required emergency endotracheal intubation and mechanical ventilation, GCS 2T. A head CT revealed a large, subdural hematoma with a midline shift. After an emergency decompressive hemicraniectomy and placement of an ICP monitor, she was admitted to the ICU with elevated ICPs and an APACHE II score of 33. On postoperative day 2 at 12:00 p.m., the patient's temperature rose to 103.5°F. The patient was placed on a cooling blanket and noted to be breathing in excess of the ventilator rate, with random extremity movement. At 12:15 p.m., a norepinephrine drip was started to maintain cerebral perfusion pressures of greater than 60 mmHg. At 12:45 p.m., her ICP increased from 42 to 62 and continued to rise over the

FIGURE 2 Blood Glucose (BG; mg/dl) and Intravenous Insulin Infusion Rate Time Series (Units/Hour) for Case Study 2



Note. Patient's BG became elevated when taken for procedure requiring higher rate of insulin infusion. BG returns to baseline and insulin infusion decreased to prior rate after patient is returned to the unit. Patient's BG spikes as patient experiences pulmonary embolism requiring adjustments to the ventilator and an increase in the insulin rate. ICP = intracranial pressure; ABG = arterial blood gas.

next few hours to the 80s. At 4:00 p.m., it was noted that the patient had lost all brainstem and cortical reflexes. Despite continued aggressive therapy, this patient expired. The mean BG for this patient was 155 mg/dl, with extreme hyperglycemia (four episodes of BG > 180 mg/dl over several hours) present on admission and at multiple times over the course of her ICU care despite intensive intravenous insulin dosage adjustment. These excursions of 145–200 mg/dl above target were clearly reflective of the severity and instability of her condition. This patient's BG variability was also 2 *SD* from the mean ($P < .001$), a level strongly associated with increased mortality (Egi et al., 2006; Krinsley, 2007) (Figure 3).

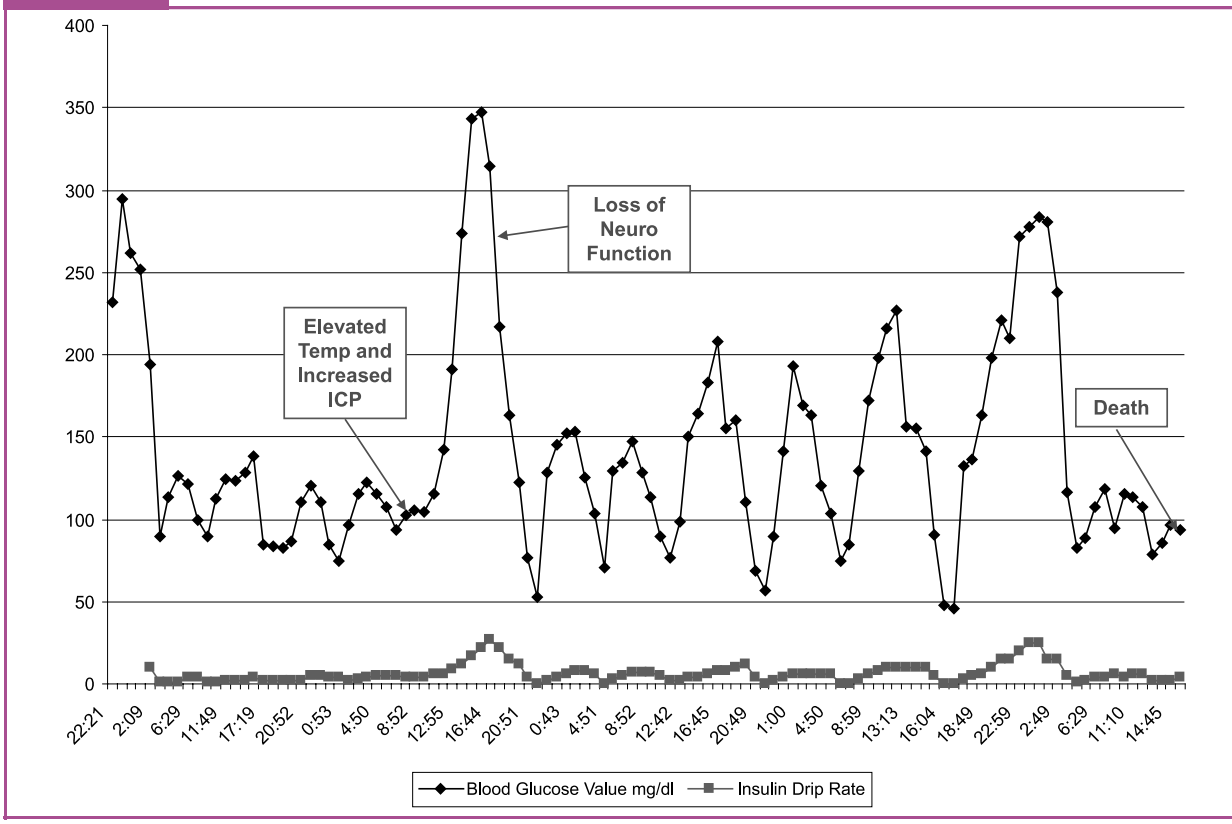
Discussion

Each of these clinical presentations describes a critically ill, nondiabetic patient who required continuous intravenous insulin therapy for hyperglycemia. Glycemic control had been achieved with a stable insulin dose for an interval before rising BG heralded worsening of the patients' clinical conditions because of life-threatening complications. In fact, the BG elevations preceded the signs and symptoms of the new condition. This type of acute BG fluctuation may be a reflection of the stress hyperglycemia and BG variability that is known to be associated with an increased risk for death (Egi et al., 2006; Krinsley, 2007) and offer early warning of clinical worsening for the bedside nurse.

In these particular cases, measurement of BG beyond the calculated mean provides a better picture of the patients' glycemic control. Although the calculated average of all BG readings or averaging the first morning BG for a patient or population can provide some insight into the degree of general BG management, wide hypo- and hyperglycemic excursions can offset each other and appear to be a successfully "normalized" BG. Conversely, a single, severe spike or drop in BG could potentially artificially raise or lower the mean BG, leading to an impression of "poor" glycemic control (Ouattara, Grimaldi, & Riou, 2006; Van Herpe, De Brabanter, Beullens, De Moor, & Van den Berghe, 2008).

The mean BG levels for these patients were 106, 112, and 155 mg/dl, respectively. However, the patients' calculated BG variance were more than 1.5 *SD* from their mean and more than 2 *SD* from the target mean in two of the cases. Indeed, their BG variation could be viewed as a reflection of their life-threatening condition. Although decreasing the mean BG is important,

FIGURE 3 **Blood Glucose (BG) and Intravenous Insulin Infusion Rate Time Series (Units/Hour) for Case Study 3**



Note. Patient with extreme BG variability due to a worsening and unresolved medical condition. BG spikes as patient loses neurological function. Extreme BG variability continues until patient progresses to brain death. ICP = intracranial pressure.

recognizing and managing BG variability with intensive insulin therapy may be an important individualized aspect of treatment of critical illness. These acute episodes of BG fluctuation may simply represent a physiological response to underlying significant clinical changes or could be viewed as sentinel events that signal impending clinical worsening, particularly after a period of control. For nursing, the BG increase or the need to increase insulin dosing to maintain BG within target range in critically ill patients may therefore be viewed as early markers of a potentially reversible state. Clearly, for nursing, these events warrant more frequent evaluation and investigation of an underlying cause and potentially offer opportunity for earlier intervention to offset the patients' decline. Further studies in BG variability would reasonably include frequency of measurement and rate and magnitude of change as well as subgroup analyses to determine clinical conditions that place patients at most risk for these dangerous fluctuations.

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References

Egi, M., Bellomo, R., Stachowski, E., French, C. J., & Hart, G. (2006). Variability of blood glucose concentration and short-term mortality in critically ill patients. *Anesthesiology*, *105*(2), 244–252.

Falciglia, M. (2007). Causes and consequences of hyperglycemia in critical illness. *Current Opinion in Clinical Nutrition and Metabolic Care*, *10*(4), 498–503.

Furnary, A. P., & Wu, Y. (2006). Clinical effects of hyperglycemia in the cardiac surgery population: The Portland Diabetic Project. *Endocrine Practice*, *12*(Suppl. 3), 22–26.

Krinsley, J. S. (2004). Effect of an intensive glucose management protocol on the mortality of critically ill adult patients. *Mayo Clinic Proceedings*, *79*(8), 992–1000.

Krinsley, J. S. (2007). Glycemic variability: A strong independent predictor of mortality in critically ill patients. *Critical Care Medicine*, *36*(11), 3008–3013.

Ouattara, A., Grimaldi, A., Riou, B. (2006). Blood glucose variability—A new paradigm in critical care? *Anesthesiology*, *105*(2), 233–234.

Reed, C. C., Stewart, R. M., Sherman, M., Myers, J. G., Corneille, M. G., Larson, N., et al. (2007). Intensive insulin protocol improves glucose control and is associated with a reduction in intensive care unit mortality. *Journal of the American College of Surgeons*, *204*(5), 1048–1054.

Umpierrez, G. E. (2007). Inpatient management of diabetes: An increasing challenge to the hospitalist physician. *Journal of Hospital Medicine*, *2*(Suppl. 1), 33–35.

Van den Berghe, G., Wilmer, A., Hermans, G., Meersseman, W., Wouters, P. J., Milants, I., et al. (2006). Intensive insulin therapy in the medical ICU. *New England Journal of Medicine*, *354*(5), 449–461.

Van Herpe, T., De Brabanter, J., Beullens, M., De Moor, B., & Van den Berghe, G. (2008). Glycemic penalty index for adequately assessing and comparing different blood glucose control algorithms. *Critical Care, 12*, R24. Retrieved from http://ccforum.com/content/12/1/R24